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Price, Malcolm

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Population excess fraction of Ectopic Pregnancy due to *Chlamydia trachomatis* in Finland

Rantsi *et al*[1] present results from a large high quality prospective population based case control study nested within the Finnish maternity cohort. In the largest ever study of its kind they examine the association between *Chlamydia trachomatis* major outer membrane protein (MOMP) peptide-specific IgG antibodies and ectopic pregnancy (EP), miscarriage, and preterm delivery. Cases for EP and miscarriage were identified through the Hospital Discharge Register from 1998-2005 and preterm delivery cases from the Finnish Medical Birth Register from 1988-2005. Controls were matched to cases by sampling time, age at serum sampling, and postal code district. The majority of subjects were aged 20-34. They found no evidence of an association between anti-chlamydial IgG antibody and miscarriage or preterm birth, however 21.0% of EP cases and 14.6% of controls were positive giving an OR in the EP cases versus matched control group of 1.56 (95% CI 1.20-2.03). Whilst this provides good statistical evidence of an association the result is difficult to interpret in terms of population burden of disease caused by CT infection. This paper investigates what this result might mean for the population excess fraction (PEF) of EP due to CT.

The PEF is the proportional reduction in disease risk that would be achieved by eliminating the exposure of interest from the population, assuming the exposure is causally related to the disease.[2] A number of formulae have been derived by which the PEF can be estimated from epidemiological data. The formula giving an estimate from case-control studies is:

$$PEF = \frac{\pi.(OR-1)}{\pi.(OR-1)+1}$$

Where OR equals the odds of exposure in the diseased (case) group divided by the odds of exposure in the non-diseased (control) group and π is the prevalence of the exposure in the population. The OR is an approximation to the incidence rate ratio and is appropriate if the disease is sufficiently rare (as is the case for EP). The presence of π in the formula reminds us that the PEF has only a "local" interpretation: it is not only a property of the disease and the exposure, but of the time and place where the data were collected. An important caveat is that the formula is only correct if there are no confounding factors or they have all been 'correctly' adjusted for.

In order to use this formula in the current context it is necessary to specify the prevalence of exposure in the population. This is not straight forward to define, and is even more difficult to estimate. Anti-chlamydial IgG antibody positivity is a proxy measure for current or previous exposure to CT (the cumulative incidence proportion). However, antibody levels often decline over time, sensitivity and specificity levels of antibody tests are imperfect, and may differ between cases and controls.[3] Furthermore, cumulative exposure depends on re-infection patterns. So population level estimates of exposure levels are difficult to obtain. In the Finnish study around 15% of controls were anti-chlamydial IgG antibody positivity. A recent study using the Dunedin New Zealand birth cohort found 24% positivity in women aged 26 using a Pgp3 double-antigen sandwich Enzyme Linked Immunosorbent Assay (ELISA) .[4]. A recent study in the UK using the less sensitive (73.8%) Pgp3 indirect ELISA assay found positivity rates of around 20-25% in women aged 23-24[5].

Based on this information PEFs can be calculated for a range of population exposure levels within which it is difficult to imagine the truth does not lie. The lower bound is chosen to be the antibody prevalence in the matched control group (15%) and sensitivity of results is assessed for exposure levels up-to a maximum level of 35%. Central estimates of PEF vary between about 8% and 16% with lower and upper 95% confidence limits varying between about 3% and 27% (table 1, column 2).

The estimates in column 2 assume the observed OR represents a fully causal relationship. However, even if CT does not cause EP we would still expect to see raised odds of exposure in the cases as the risk factors for CT exposure are the same as some of the other causes of pelvic inflammatory disease (PID) (such as other STI's) and hence for EP. So these PEFs should be viewed as upper bounds. Quantification of the level of confounding in the estimated OR is difficult as the study authors had no information on confounding factors. However, a recent paper applying finite mixture model (FMM) techniques to anti-CT IgG antibody level data in cases with tubal factor infertility (TFI) and pregnant controls in the UK found the effects of confounding could lead to an overestimate of PEF of anything up-to 60% in this group[6]. The titre distributions in cases and controls were modelled as a mixture of several component distributions. The causal mechanisms for TFI were attributed to differences between cases and controls in specific components, rather than differences in overall antibody prevalence, reducing the extent to which PEF estimates are vulnerable to confounding. This same adjustment applied to the PEFs calculated above gives central estimates ranging from 5% to 10% with lower and upper confidence limits between 2% and 16% (table 1, column 3). However, this is likely an over-adjustment so these estimates should be regarded as lower bounds .

A recent report estimated the PEF of EP due to CT in the UK in the early 2000's to be about 5%.[7] The UK analysis did not account for the greater than additive effect of multiple PID episodes on EP risk observed in prospective studies which might raise it to around 8%. Different PEFs are not directly comparable as they are time and place specific. However, the EP data from the Rantsi *et al*[1] study cover the period 1998-2005, a similar time frame to the UK work. There is some evidence based on positivity rates in CT tests that population chlamydia exposure may have been higher in Finland than in the UK during this period.[8] Which may explain why the PEF estimate for Finland is slightly higher than for the UK. However, whilst it is difficult to know, there is likely to be at least a reasonable degree of homogeneity in risk patterns across most of Western Europe, a view supported by the relatively close agreement between these two sets of estimates.

Both the UK report and the analysis here suggest that previous estimates of the PEF of EP due to CT of up-to 25%[9] likely overestimate the importance of CT on the population burden of EP. In the present case, one would have to propose fairly extreme assumptions about exposure prevalence, confounding, and the direction and size of sampling error to obtain a PEF that is even close to this. Overall it seems likely that PEFs of EP due to CT generally lie between around 5% and not much more than 10%. If salpingitis is the only causal pathway through which CT can cause EP this is consistent with recent estimates of the PEF of salpingitis due to CT of around 20%, and the PEF of EP due to salpingitis of around 30% for the same period in the UK.[7]

The excellent study by Rantsi *et al*[1] has added valuable new data for understanding the role of CT in the etiology of EP. The analysis here is based upon assumptions about population exposure patterns and confounding. It may be possible to obtain a more robust estimate of PEF for this population

through direct application of FMM methods to the raw MOMP absorbance data. Such a methodology avoids the need to estimate population exposure prevalence and mitigates the effect of unmeasured confounding on the estimates[6].

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Table 1. Estimated unadjusted and adjusted PEFs of EP due to CT (95% Confidence limits) in Finland for different assumed population exposure proportions.

Assumed proportion of population ever exposed	PEF (95% CI) unadjusted	PEF (95% CI) adjusted*
0.15	7.7% (2.9%,13.4%)	4.6% (1.7%, 8.0%)
0.2	10.1% (3.8%,17.1%)	6.0% (2.3%,10.2%)
0.25	12.3% (4.8%,20.5%)	7.4% (2.9%,12.3%)
0.3	14.4% (5.7%,23.6%)	8.6% (3.4%,14.2%)
0.35	16.4% (6.5%,26.5%)	9.8% (3.9%,15.9%)

Adjusted PEF assumes the unadjusted PEF overestimates by 60% (see text)[6]